

Positron emission tomography/computed tomography scan of Vogt–Koyanagi–Harada syndrome with associated autoimmune thyroid disease

A case report and literature review

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Abstract

Rationale: Vogt–Koyanagi–Harada (VKH) syndrome is a rare disease and could be associated with autoimmune thyroid disease (AITD). This report was aimed to investigate the utility of ¹⁸F-fluodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) for the diagnosis of VKH syndrome with AITD and to perform a literature review on the association between the 2 diseases.

Patient concerns: A 55-year-old woman without the history of ocular trauma suffered from chronic headache. She was presented with painful blurred vision of both eyes with headache for 2 weeks. Ophthalmic evaluations revealed panuveitis, exudative retinal detachment, and papilloedema in both eyes. The clinical symptoms and presentations are compatible with the diagnosis of VKH syndrome. Other examinations for intraocular infection, malignancy, and lupus choroidopathy were of negative results. The result of contrast-enhanced computed tomography (CT) of the brain was normal. Due to the history of cancer in the patient's families, a ¹⁸F-FDG PET/CT whole-body scan was performed. The result indicated a focal of 2-fluoro-2-deoxy-D-glucose (FDG) uptake at the right upper lobe of the thyroid. Therefore, the patient's thyroid function was examined and the result indicated euthyroidism with detectable thyroid peroxidase/thyroglobulin antibodies.

Diagnoses: VKH syndrome with associated AITD.

Interventions: Treatment with intravenous pulse systemic methylprednisolone (1000 mg daily) was prescribed for 3 days and then shifted gradually to tapered oral steroid medication.

Outcomes: Symptoms of papillitis and serous retinal detachment of VKH syndrome was relieved after steroid treatment

Lessons: ¹⁸F-fluodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) can be used for the effective diagnosis of VKH syndrome with AITD.

Abbreviations: ¹⁸F-FDG PET/CT = ¹⁸F-fluodeoxyglucose positron emission tomography/computed tomography, AITD = autoimmune thyroid disease, BCVA = best corrected visual acuity, CT = computed tomography, CTLA-4 = cytotoxic T lymphocyte-associated antigen 4, FDG = 2-fluoro-2-deoxy-D-glucose, OCT = optical coherence tomography, PET = positron emission tomography, SNPs = single nucleotide polymorphisms, TPO-Ab/Tg-Ab = thyroid peroxidase and thyroglobulin antibodies, VKH = Vogt–Koyanagi–Harada.

Keywords: autoimmune thyroid disease, positron emission tomography/computed tomography, Vogt–Koyanagi–Harada syndrome

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1. Introduction

Vogt–Koyanagi–Harada (VKH) disease is a bilateral granulomatous panuveitis with exudative retinal detachments and papilloedema. Systemically, it may be presented with multisystemic symptoms such as meningismus (neurological manifestation), tinnitus, hearing impairment, vertigo, alopecia areata, and poliosis (integumentary manifestation).^[1] The diagnostic criteria for VKH syndrome can be categorized into 3 sets including probable VKH (with only ocular manifestation), incomplete VKH (ocular finding with neurological and/or integumentary manifestation), and complete VKH (ocular finding with neurological and integumentary manifestation). The classification of VKH depends on how much of the presentations fulfilled these criteria.^[2] In previous reports, VKH syndrome has been shown to associate with autoimmune thyroid disease (AITD).^[3–8] The AITD is characterized by the dysfunction of thyroid tissue by antibody-mediated immune inflammation and the etiology of AITD is multifactorial and occurs predominantly in females.^[9]

Positron emission tomography (PET) is a functional imaging technique for the detection of malignancy. It is also widely used in inflammatory diseases and other fields of medicine. The reagent ¹⁸F-fludeoxyglucose (FDG) is a glucose analog that is an important imaging modality for the detection of tumor staging, restaging, recurrence; and the monitoring of treatment response.^[10] The combination of PET and computed tomography (CT) can provide molecular biological function and anatomic information for the goal of medical surveillance. Incidental focal FDG thyroid uptake obtained from the PET examination could be used to determine malignancy or incidentaloma,^[11,12] and AITD.^[13–15] Further examination such as ultrasound fine-needle

aspiration biopsy is suggested for the evaluation of these lesions identified by PET/CT.

In this study, we reported a rare case of incomplete type VKH syndrome accompanied with AITD. There are few reports about both diseases and the association of both diseases was not clear until now.^[3–8] Furthermore, we demonstrated ¹⁸F-FDG PET/CT can be used as an alternative method for diagnosing possible comorbidity of VKH syndrome.

2. Case presentation

The informed consent was obtained from this patient.

A 55-year-old Taiwanese woman was presented to our hospital with binocular decreased visual acuity that is associated with headache and nausea in the previous 2 weeks. The patient has no history of trauma or ocular surgery. Her best corrected visual acuity (BCVA) was 2/60 in the right eye and 3/60 in the left eye. The intraocular pressure was 14 mm Hg in both eyes. Slit-lamp examination revealed congested conjunctiva, clear cornea, cells, and flares in the anterior chamber. Dilated fundus examination demonstrated exudative retinal detachment, papillitis, and vitritis in both eyes (Fig. 1 A and B). There was subretinal fluid accumulation with retinal detachment and thickening of choroid determined by optical coherence tomography (OCT) (Fig. 1C and D). Fluorescein and indocyanine green angiography determined hyperfluorescence and disseminated spotted choroidal hyperfluorescence (Fig. 2). The clinical differential diagnosis at the time included VKH syndrome, intraocular infection, malignancy, lupus choroidopathy, and brain tumor. There was no other auditory/integumentary manifestation noted. The results of serological markers for inflammation, autoimmunity, and

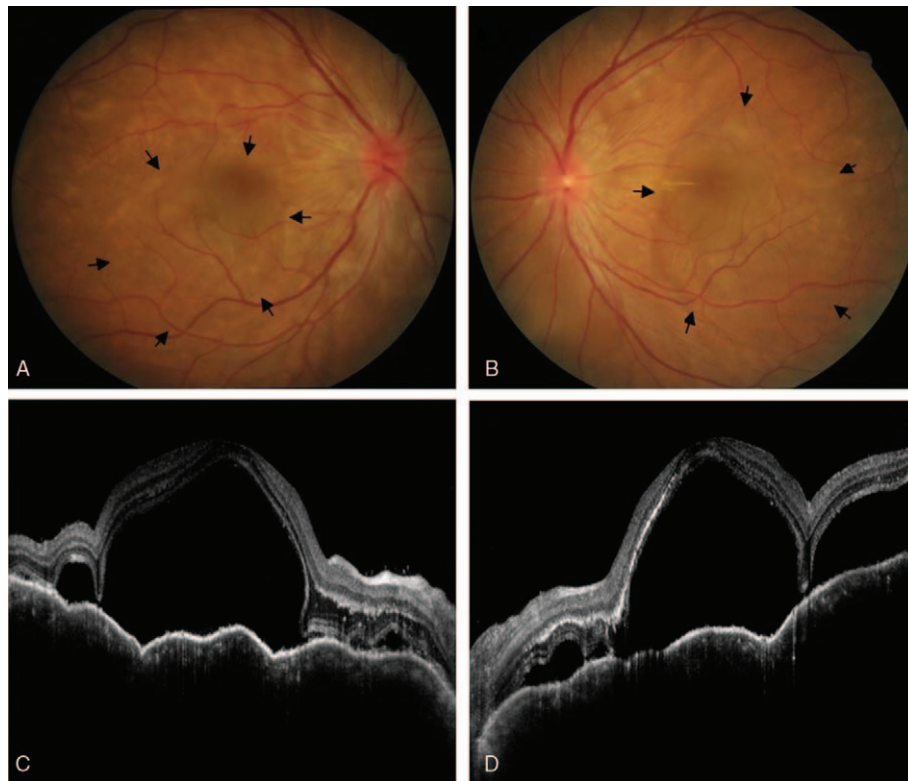


Figure 1. Fundus photography and optical coherence tomography (OCT) of both eyes at the initial visit. (A and B) Fundus photography showed papillitis and posterior pole exudative retinal detachment bilaterally (arrow). (C and D) OCT of macula showed subretinal fluid accumulation with retinal detachment and thickening of choroid.

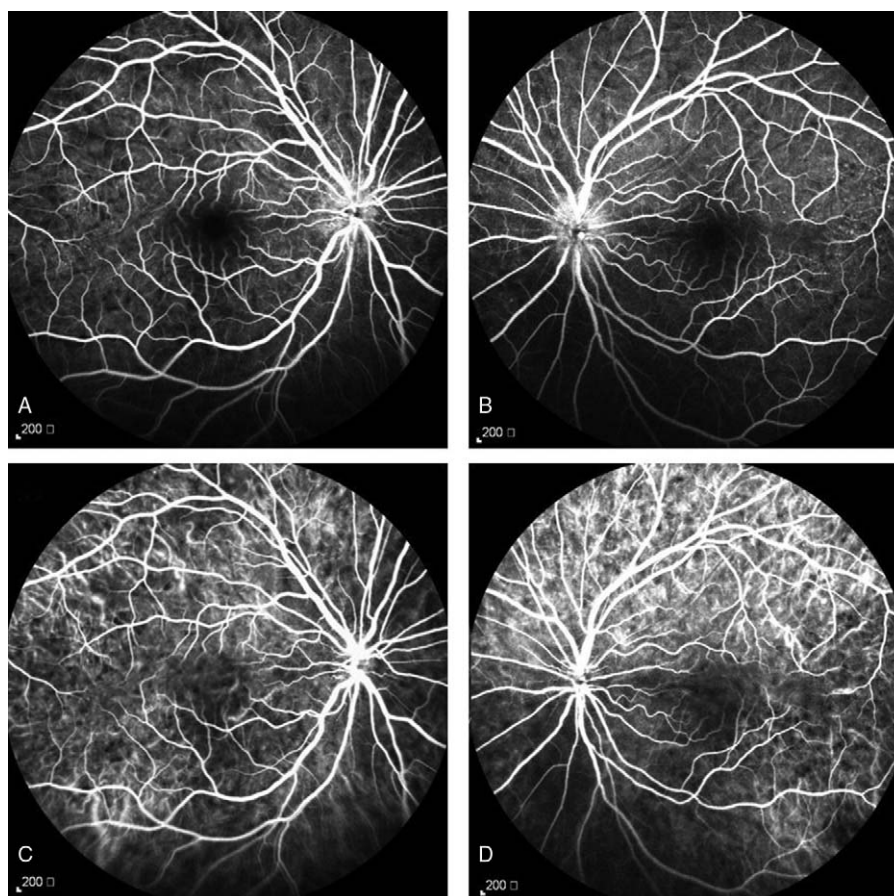


Figure 2. Fluorescein angiography (FAG) and indocyanine green angiography (ICG) performed at the initial visit. (A and B) FAG showed multiple pinpoint leakages in the arteriovenous phase, with optic disc hyperfluorescence. (C and D) ICG showed segmental leakage.

infection were negative. Review of systems was normal except the history with headache and nausea. Contrast-enhanced computed tomography (CT) of the brain also indicated negative findings. Because patient had a family history of cancer, a whole body PET/CT scan was arranged to rule out possible underlying diseases. The analysis revealed a focal FDG uptake at the right upper lobe of thyroid (Fig. 3). Serological tests for malignancy were negative, whereas thyroid peroxidase and thyroglobulin antibodies (TPO-Ab/Tg-Ab) levels were elevated. The result of ultrasound assisted fine-needle aspiration biopsy of thyroid nodule indicated inflammatory cells without evidence of malignancy.

According to the clinical findings, serological and image examination, a diagnosis of VKH syndrome accompanied AITD was diagnosed. The patient underwent intense pulse methylprednisolone therapy (1000 mg daily) for 3 days, and followed by oral prednisolone at 1 mg/kg/day. The oral steroid was tapered when ophthalmological improvement was achieved gradually. Two months after the acute attack of VKH syndrome, the patient was presented improvement of the symptoms. Her BCVA recovered to 6/12 in right eye and 6/6.7 in left eye. Fundus examination showed reattached retina in both eyes, and the results of OCT scanning revealed that the serous retinal detachment had resolved in both eyes (Fig. 4).

3. Discussion

In the case presented in this study, a middle-aged woman was presented with blurred vision of both eyes and headache for 2

weeks. Ophthalmic evaluations revealed panuveitis, exudative retinal detachment, and papilloedema in both eyes. The clinical symptoms and signs are compatible with the diagnosis of VKH syndrome. The results of other diagnostic examinations such as intraocular infection, malignancy, and lupus choroidopathy were negative. Because of the patient's family history of cancer, a ^{18}F -FDG PET/CT whole-body scan was performed. The PET/CT result revealed a focal FDG uptake at the right upper lobe of the thyroid. The serological test showed euthyroidism with detectable thyroid peroxidase/thyroglobulin antibodies. The results of sono-guide aspiration biopsy showed no malignancy. Therefore, the diagnosis of AITD was made. As we known, VKH syndrome with associated autoimmune disorders are reported in previous literatures,^[3-8] and the further evaluations of the underlying autoimmune disease with VKH syndrome were suggested for improving diagnostic accuracy and therapeutic outcome.

The VKH syndrome is an autoimmune systemic disease and it may be combined with neurologic, auditory, and cutaneous manifestations.^[1] It is common for VKH syndrome to occur in patients with genetic predispositions to the disease, including those from Asia, Latin America, and the Middle East.^[1] The role of genetic factors in the development of VKH, such as HLA alleles, CTLA-4, and other polymorphisms of genes had been identified and studied, however, the importance of these genomic findings are currently unclear.^[1] There are 4 phases in the presentation of VKH syndrome, including prodromal, acute uveitic, convalescent, and chronic recurrent phases. Symptom such as dermatologic changes commonly occur in later convalescent in

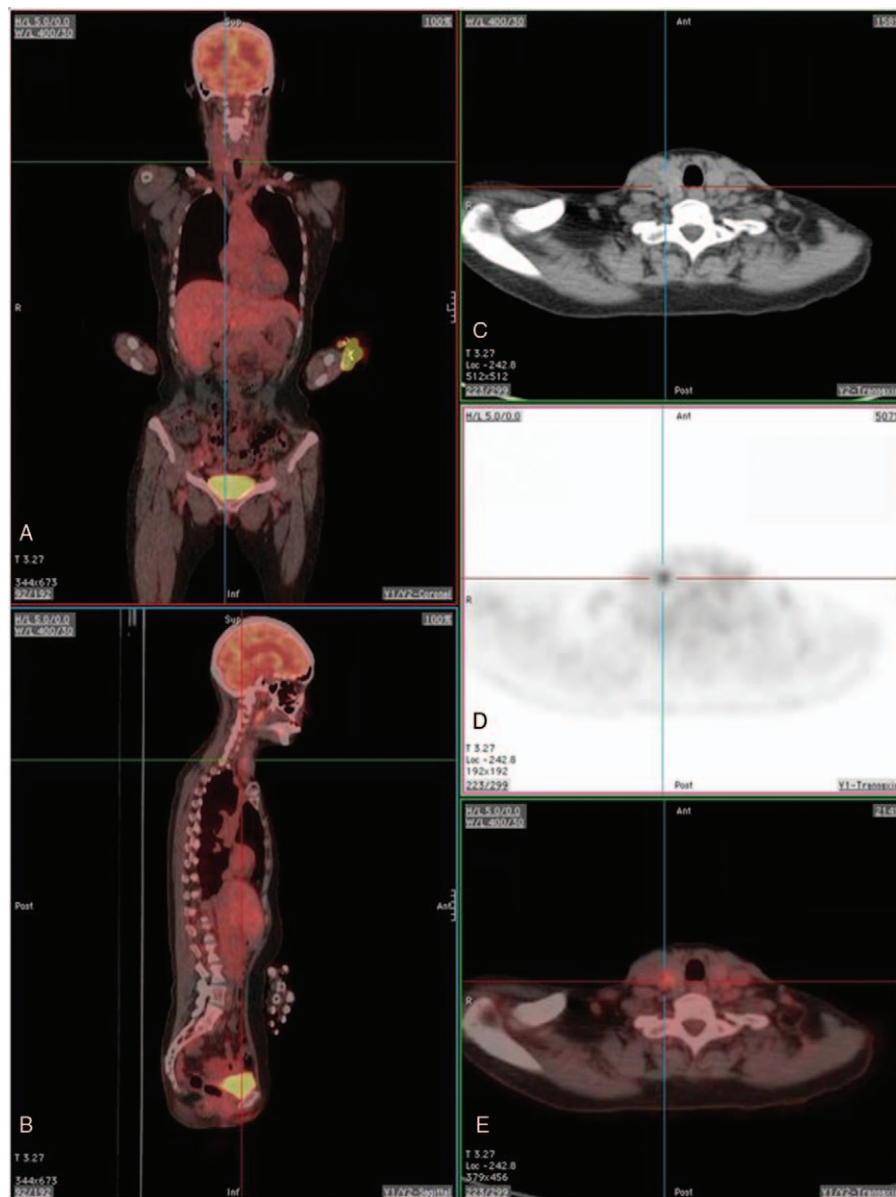


Figure 3. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) for whole-body evaluation. (A) Coronal fused PET/CT; (B) sagittal fused PET/CT; (C) transverse CT; (D) transverse PET; (E) transverse fused PET/CT. PET/CT showed focal uptake of tracer in the right upper lobe of thyroid.

chronic phase.^[1] In 2011, Rao et al^[16] compared 1147 patients with bilateral uveitis in 10 centers, 180 of these patients were diagnosed with VKH syndrome with extremely high positive association to exudative retinal detachment. More than half of these patients with acute VKH syndrome presented only ocular manifestation.^[17] However, there is still need to differentiate VKH syndrome from other causes of panuveitis, including, sympathetic ophthalmia, infectious intraocular inflammation, intraocular lymphoma, posterior scleritis, uveal effusion syndrome, sarcoidosis, and other systemic disorders.^[1] Therefore, it is always necessary to evaluate the patient's complete history, systems and physical examinations, and laboratory results. In our case, systemic evaluation and laboratory testing results were normal. The clinical and angiographic features in both eyes were determined to be typical for the acute phase of VKH syndrome.

The technique of ^{18}F -FDG PET/CT is commonly used for tumor staging, restaging, detection of recurrence, and the

monitoring of treatment response. Additionally, FDG could also accumulate in inflamed or infected tissues,^[18] diffused FDG uptake in the thyroid is likely to be normal physiology of thyroiditis. The focused accumulation of FDG, however, has a high chance of malignancy (range around 10–64%),^[12,14,18] where fine-needle aspiration for cytological examination is strongly recommended for these cases. Park et al have reported a case that 47-year-old man was diagnosed of VKH syndrome with brain involvement via PET/MRI, revealing multifocal FDG uptake areas along the cerebral sulci that is compatible with clinical seizure symptoms.^[19] Compared to the previous report,^[19] there was no tracer uptake area in the brain for our patient, yet, a thyroid lesion was found. The diagnosis of AITD was eventually made due to the lack of malignant tumor markers from the tissue biopsy, and elevated TPO-Ab/Tg-Ab titers in the serological test. It was presumed that the comprehensive PET/CT evaluation can provide more detailed

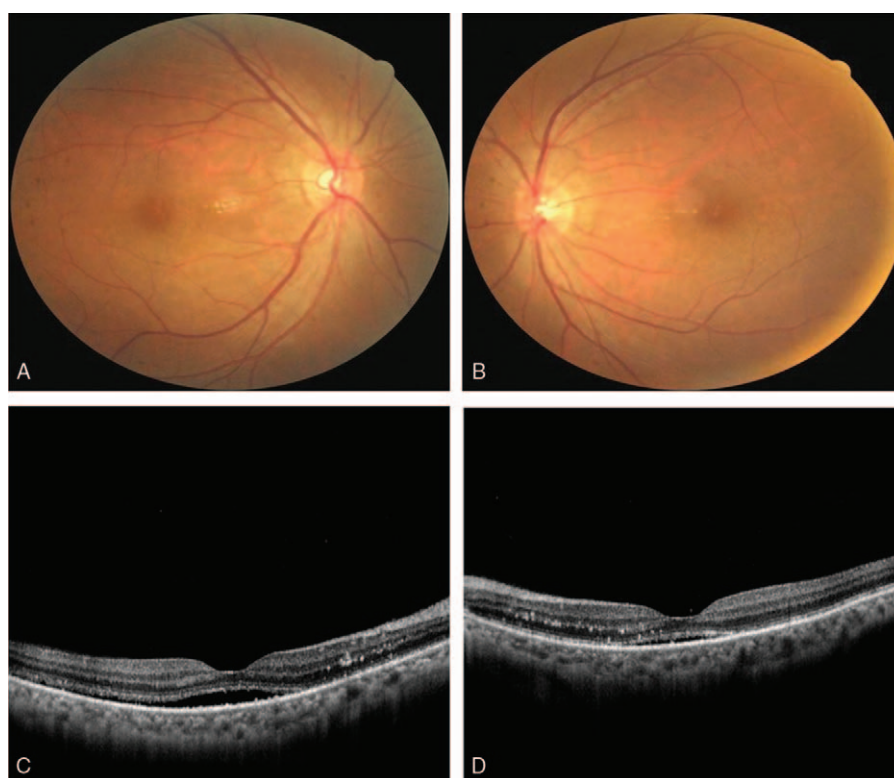


Figure 4. Fundus photography and optical coherence tomography (OCT) of both eyes performed 2 months later. (A and B) Fundus photography showed reattached retina and papillitis was resolved. (C and D) OCT showed reattached retina with minimal residual subretinal fluid after steroid therapy.

information for determining the underlying disease associated with VKH syndrome.

In literature reviews, the association of VKH syndrome with AITD has been reported in 6 cases (5 woman out of 6, aged between 20 and 65 years).^[3–8] In these reports, 4 of them were determined with hypothyroidism and elevated TPO-Ab/Tg-Ab titers,^[3,4,6,8] and 2 of them were of hyperthyroidism.^[5,7] Drug-induced hypersensitivity is considered as a triggering factor for T cell-mediated autoimmune dysfunction to induce Grave disease followed by VKH syndrome.^[7] It was also reported that VKH syndrome and Hashimoto thyroiditis may share a basic defect in the autoimmune pathogenetic process.^[3] The HLA alleles was also considered as a factor that can trigger VKH syndrome associated with autoimmune polyglandular syndrome type 1.^[5] In addition, another report has demonstrated that a 45-year-old Saudi man of VKH syndrome associated with hypothyroidism and diabetes mellitus. They considered that the pathogenesis of VKH syndrome can include microbial agent or antigen to alter cell surface component of skin, uvea, follicular epithelial cell of thyroid, and pancreas that can trigger autoimmunogenic organ dysfunctions.^[4] Compared to the previous reports,^[3–8] our case was presented with VKH syndrome accompanied with AITD characterized by euthyroid with elevated TPO-Ab/Tg-Ab titers. The TPO-Ab titers are frequently presented in euthyroid subjects with prevalence 12% to 26%, and it could be identified as a risk factor for hypothyroidism.^[20]

The etiology of VKH syndrome and AITD were both multifactorial and some previous literatures have reported the possible correlations between them. First of all, they are both caused by T cell-mediated autoimmun reactions. Secondly, the both of them commonly occur in women during their second to

fifth decades of age.^[1,9] Thirdly, previous reports demonstrated that virus may mimic tissue antigens to trigger autoimmune reaction in VKH syndrome and AITD.^[21,22] Finally, there are similar genetic factors that can be associated with the pathogenesis of VKH syndrome and AITD. In a study performed by Du et al, 209 Chinese Han patients with VKH syndrome were compared with 256 healthy controls. It was determined that the allele frequency of single nucleotide polymorphisms (SNPs) +49 of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) was significantly higher in the patients with VKH syndrome. Other haplotypes of CTLA-4 such as –1661A:–318C:+49G:CT60G were also determined in this study to be associated with VKH syndrome.^[23] Ueda et al^[24] reported SNPs +49 and CT60 of CTLA-4 are associated with AITD risks. According to these previous literatures,^[23,24] the CTLA-4 haplotype may play an important role for the simultaneous trigger of VKH syndrome and AITD. Although genetic susceptibility studies are helpful in understanding the pathogenesis of VKH, however, their role in the diagnosis and management of VKH remain uncertain. Therefore, further studies are required to investigate the importance of polymorphism for the diagnosis of VKH.

As above described,^[23,24] several studies have demonstrated the association of VKH syndrome and AITD by genetic analysis. Currently, the technology and machine for genetic analysis is still not popular in all hospital. According to this case, we provided another method, PET/CT scan, to find the patient with VKH syndrome and AITD. This method could indirectly screen the patient with VKH syndrome to find out whether the patient underwent AITD or other diseases. However, further studies to include more cases will provide more evidences about the role of PET/CT scan in the possible connection between VKH syndrome and AITD.

In conclusion, our report presents a rare case of VKH syndrome associated with AITD, diagnosed by ^{18}F -FDG PET/CT scanning. Therefore, it is recommended that ^{18}F -FDG PET/CT scan may be a potential noninvasive tool for the clinical diagnosis of VKH syndrome associated AITD.

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